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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/362,598	07/28/1999	JOEL V. WEINSTOCK	3948/79934	7062

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EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/362,598	Applicant(s) WEINSTOCK ET AL.	
	Examiner Robert A. Zeman	Art Unit 1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 09 December 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The reply was filed after the date of filing a Notice of Appeal, but prior to the date of filing an appeal brief. The Notice of Appeal was filed on *09 December 2004*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *see attached*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *24, 26 and 28-32*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached..
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

ADVISORY ACTION

The amendment filed 12-9-2004 under 37 CFR 1.116 in reply to the final rejection has been considered but is not deemed to place the application in condition for allowance and will not be entered because: The proposed amendment raises new issues that would require further consideration and/or search.

The declaration filed on 12-9-2004 will not be considered because good and sufficient reasons why it was not earlier presented have not been shown.

Claim Rejections Maintained

Applicant's arguments have been fully considered. However, since said arguments are predicated on amendments not made of record they are deemed non-persuasive. Consequently, all pending rejections are maintained for reasons of record and are reiterated below.

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 24, 26 and 28-32 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of determining the immune response the co-infection of mice with *M. avium* and *S. mansoni* (either with or without TNBS treatment) or the infection of mice with *T. muris* (with TNBS treatment) by determining the

amounts of IL-4, IL-5 and IFN-γ, does not reasonably provide enablement for a method of screening an helminthic parasite preparation for one or more components that reduce excessive Th1 immune responses, wherein said preparation is prepared by fractionating and sub-fractionating the helminthic preparation is maintained for reasons of record. The specification still does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues:

1. Only claim 26 recites the limitations "sub-fraction" or "testing of a sub-fraction in claim 26. Hence, any rejection based on lack of enablement regarding sub-fractions cannot apply to claims 24 and 28-30.

2. The specification teaches sub-fractionation at page 32, lines7-11.

3. The specification describes fractionation on page 32, lines 4-6.

4. Iterative fractionation and testing of resulting sub-fractions for activity is a well-known and routine method for isolating biologically active components(s) of a complex biological mixture.

5. Palczewski et al. disclose an iterative sub-fractionation approach to purify rhodopsin kinase.

6. Soubeyrand et al. et al. disclose an iterative sub-fractionation approach to purify a Phospholipase A2 enzyme.

7. Ostergaard et al. et al. disclose an iterative sub-fractionation approach to purify L-Glactono-γ-Lactone Dehydrogenase (GLDase).

8. Ma et al. et al. disclose an iterative sub-fractionation approach to purify an Electron-transfer Flavoprotein:Rhodoquione Oxidoreductase (ETF-FO).

9. The specification provides guidance on assays and determination of a Th1 response at a number of places including page 21, line 21 to page 24, line 22 and in Examples.

10. It is not necessary for the specification to describe more than one assay that would function to measure a Th1 immune response in order to be enabling. Thus, the description of assays for IFN-γ, TNF-α and IgG2a are sufficient to meet the enablement requirement with regard to the determination of a Th1 immune response as required by the instant claims.

11. The purified immunomodulatory component(s) identified by the fractionation approach will result in identifying one or more components that reduce an excessive Th1 response.

12. The specification provides guidance with regard to *in vivo* assays at page 30, line 34 to page 34, line 20 and in the Examples.

13. The specification teaches specific animal models for assaying the effect of a HH fraction on an excessive Th1 immune response in Table 1.

14. Example 8 provides details on the use of the mouse EAE model of MS to investigate the effect of schistosomes on autoimmune disease.

15. Attenuation of a Th1-type gut inflammation in mice by treatment of helminthes is shown in Example 3.

16. The specification states in Example 3 that "Injections of HH may prevent any of the autoimmune or excessive inflammatory diseases listed in Table 1". Hence, one would assay the effect of a fraction or sub-fraction of HH by injecting it into an animal that models disease and monitors symptoms.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard, to Point 1, the Office agrees with Applicant's assertion that only claim 26 recites the limitations "sub-fraction" or "testing of a sub-fraction in claim 26. However, since the aforementioned rejection is based on the lack of enablement regarding both "fractions" and "sub-fractions" the rejection is deemed valid and hence is maintained.

With regard to Points 2-4, the Office agrees with Applicant's assertion that the methods of obtaining fractions and sub-fractions claimed in the instant claims and iterative methods constitute methods known in the art and hence would have been obvious to one of ordinary skill in the art. However, said methods are not sufficient to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make **and use** the invention commensurate in scope with these claims.

With regard to Points 5-8, the cited references are drawn to methods of purification. Since the instant claims are drawn to methods of screening helminthic parasite preparations for components that reduce an excessive Th1 response, the cited references are not germane and hence are not persuasive.

With regard to Points 9-11, while the specification prophetically discusses the testing of fractions and sub-fractions, it does not disclose how said **fractions and sub-fractions** were used in the assay. Moreover, the specification does not provide guidance as to which biological functions (other than IL-4, IL-5, IgE, IgG1, IgG2a, TNF-α and IFN-γ production) should be tested or **how the testing of said functions would result in identifying "one or more components that reduce an excessive Th1 response"**. The specification gives not guidance as to what degree a given "biological function" has to be enhanced (or inhibited) in order to be deemed to have "reduced an excessive Th1 response. Moreover, the specification does not even

give guidance as to what constitutes an "excessive Th1 response" with regard to given "biological activity". Finally, the purification of a given component by the fractionation approach would not determine whether said component reduces an excessive Th1 response since the specification provides no correlation between the biological activity of a given component and the effect, if any, it would have on an excessive Th1 response.

With regard to Point 12, the specification is silent on how one would perform the "assay" step of the claimed methods *in vivo*. The specification provides no guidance on what specific "biological activities" are measured, how said "biological activities" are measured or even how samples are obtained. Finally, the specification is silent on **how the testing of said functions would result in identifying "one or more components that reduce an excessive Th1 response".** Given the total lack of guidance provided by the specification it would require undue experimentation by one of skill in the art to make and use the invention commensurate in scope with the claimed subject matter.

With regard to Point 13, Table 1 merely recites Animal models useful in the study of certain treatable diseases but fails to provide guidance as to how said animal models to be used in the claimed methods.

With regard to Points 14-15, while Example 8 provides details on the use of the mouse EAE model of MS to investigate the effect of schistosomes on autoimmune disease and Example 3 demonstrates the attenuation of a Th1-type gut inflammation in mice by treatment of helminthes, neither demonstrates how the results of the exemplified methods could be correlated with identifying "one or more components that reduce an excessive Th1 response".

With regard to Point 16, one cannot conclude that the skilled artisan would correlate the statement that "Injections of HH may prevent any of the autoimmune or excessive inflammatory diseases listed in Table 1" with assaying the effect of a fraction or sub-fraction of HH by injecting it into an animal that models disease and monitors symptoms. The aforementioned statement merely contemplates the possible effect of HH injections on autoimmune or excessive inflammatory diseases.

Therefore, for the reasons set forth above the specification is only enabling for an *in vitro* method of determining which helminthic fractions or sub-fractions can affect the an immune response in mice co-infected with *M. avium* and *S. mansoni* (either with or without TNBS treatment) or the infection of mice with *T. muris* (with TNBS treatment) by determining the amounts of IL-4, IL-5 and IFN-γ.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The instant claims are drawn to a method of screening a helminthic preparation for one or more components that reduce an excessive Th1 immune response. The method comprises preparing and fractionating the preparation and assaying the products for the ability to reduce an excessive Th1 immune response.

The rejection of claims 24, 26 and 28-32 under 35 U.S.C. 103(a) as being unpatentable over Pearce et al. (Journal of Exp. Medicine, Vol.173, pages 159-166, 1991) in view of Pearce et al. (PNAS, Vol. 85, pages 5678-5682, 1988) is maintained for reasons of record.

Applicant argues:

1. Pearce et al. (1991) provides no motivation to screen a helminthic parasite preparation for one or more components that reduce an excessive Th1 immune response because it focuses on the beneficial aspects of stimulating Th1 function.

2. The fact that the claims are drawn to screening assays and not to methods of reducing an excessive Th1 response is irrelevant to the alleged obviousness of the claimed invention over the cited references. The context of the references must be still considered in arriving at any motivation to combine the teachings of the references. Since there is no recognition in the cited references that a Th1 immune response is something to avoid, there is no reason one of skill in the art would screen a helminthic parasite preparation for one or more components that reduce an excessive Th1 immune response.

3. There is no teaching in either reference of an "excessive" Th1 immune response so there

4. Neither reference discloses the claimed method, nor can they be combined in such a way as to render obvious said method.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1, 2 and 4, Applicant is reminded that, the instant claims are drawn to a method of screening a helminthic preparation for one or more components that reduce an excessive Th1 immune response. Pearce et al. (1991) disclose a method of measuring various Th1 and Th2 hallmarks. Said method identifies both Th1 enhancers as well as Th1 inhibitors. Hence, the disclosed method comprises preparing and fractionating the preparation and assaying the products for the ability to reduce an excessive Th1 immune response. Moreover, Pearce et al. (1991) discloses that infected mice had a down regulation of Th1 responses (see page 164). Hence, one of skill in the art would have been motivated to identify what stimulus was responsible. The use to which said data would be put is irrelevant since the stated goal of the instant claims was to **identify** one or more components that reduce an excessive Th1 immune response.

Consequently, as outlined in the previous Office action, **Pearce et al. (1991)** disclose a method of identifying antigens from the helminthic parasite *Schistosoma mansoni* for the ability to reduce Th1 responses (see abstract and **pages 164-165**). Said method comprises preparing parasite antigens e.g. cercariae, soluble extracts of schistosomula, adult worms and eggs (see Material and Methods section, page 160) and screening those preparation for the production of either IFNγ (Th1 response cytokine) or IL-5 (Th2 response cytokine)(see figures 1, 5 and Tables 2-3). Pearce et al. (1991), contrary to Applicant's assertion, clearly disclose, "Th2 response in

infected animals was shown to be induced by schistosome eggs and directed largely against egg antigens" (see abstract lines 10-12). Therefore, **the method disclosed by Pearce et al. (1991)** differs from the claimed invention in that they do not explicitly disclose a method of preparing an helminthic parasite antigen comprising homogenizing, separating homogenate fractions and identifying sub-fractions for biological activity. However, Pearce et al. (1988) disclose a method of preparing antigens from *Schistosoma mansoni* that comprises obtaining adult schistosomes, homogenizing in phosphate buffered saline, centrifuging and purifying by immunoaffinity chromatography (see pages 5678-5679). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare Schistosoma antigens utilizing the homogenization and immunoaffinity column chromatography disclosed by Pearce et al. (1988) and assay the resulting fractions for the ability to reduce excessive Th1 responses utilizing the assay methods disclosed by Pearce et al. (1991). It would have been expected, barring evidence to the contrary, that the purified schistoma antigens would be identified for their ability to reduce excessive Th1 responses because Pearce et al. (1991) specifically identify and compare antigens and their abilities to down regulate Th1 cytokine production. It should be noted that Applicant has maintained that the homogenization and sub fractionation of a helminthic preparation is well known in the art and hence would be obvious to one of ordinary skill in the art.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: those steps required for "detecting a Th1 response in said mammal".

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert A. Zeman
February 2, 2005

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